

Beta-Lactam allergies and the role of penicillin skin testing

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Beta-Lactam allergies and the role of penicillin skin testing

■ **Penicillin skin testing**

- Is useful in predicting IgE mediated reactions to penicillin class antibiotics.
- Need to be followed by an oral challenge if skin test negative
- Does not help predict cephalosporin or other beta-lactam reactions and should not be done for these indications.

■ **Cephalosporin skin testing**

- Is only useful in predicting specific IgE mediated reactions to the specific cephalosporin used for testing.

■ **Other Beta-lactam skin testing**

- Is only useful in predicting specific IgE mediated reaction to the specific other beta-lactam used.

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- Who can you test or challenge?
 - Patients who have a history of anaphylaxis, respiratory problems, hives, local swelling at the site of injection, other rashes, gastrointestinal symptoms, unknown index symptoms, and other mild symptoms not specifically excluded below
- Who should not be tested or challenged?
 - Anyone with a history compatible with Stevens-Johnson Syndrome, toxic epidermal necrolysis, hemolytic anemia, nephritis, severe hepatitis, or oral and/or skin blisters associated with or attributed to previous penicillin class antibiotic use

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- Patients with a history of penicillin allergy who are skin test negative will have an adverse reaction about 3% of the time to any oral antibiotic
- Cephalosporins are safely used in penicillin skin test positive individuals.
- Penicillin allergy is becoming less frequent. Currently less than 5% of history positive individuals are skin test-positive or oral challenge-positive if skin test-negative

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- Oral challenges are a safe way of evaluating children with most beta-lactam associated rashes Cephalosporins are safely used in penicillin skin test positive individuals.

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- Commercial anti-penicillin FEIAs (Phadia)
 - Penicilloyl G – c1
 - Penicilloyl V – c2
 - Amoxicilloyl – c6
- Very poor correlation to skin test and oral challenge results
- Not clinically useful

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- Reactions to oral penicillins in skin test positive individuals can start up to 24 hours after ingestion
- Females are not more likely to be penicillin skin test positive than males if 5 mm is used as the cut off for a positive penicillin skin test
- Puncture positive individuals are extremely allergic and have high rates of testing associated reactions.

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- Use Pre-Pen as supplied.
- Use native penicillin at 0.01 molar
- Use amoxicillin at 0.01 molar (3.6 mg/ml)
- The high rates of false positives noted in the European literature is associated with using amoxicillin at 20 to 25 mg per ml which is 6 to 7 time more concentrated than recommended. The limit of solubility of amoxicillin in water at pH = 7 is 4 mg/ml.
- Use cephalosporins and other beta-lactams at 0.01 molar.

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- Oral challenge are essential after skin testing to avoid false negative skin testing and to identify T-cell mediated reactors
- Skin testing with the minor determinants, penicilloate and penilloate, is not necessary.
- Challenge with amoxicillin 250 mg orally and observe for 1 hour
- Give an oral challenge prior to parenteral penicillin use
- Delayed onset T-cell reactions typically occur within 2-3 days.

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■ Potassium Penicillin G

- FW = 372.48 gm/mole
- Supplied as 5 million unit vials = 3.134 gm
- 1mg of Potassium Penicillin G = 1595 units
- 0.01 Molar Potassium Penicillin G = 3.725 mg/ml or 5941 units/ml
- Can be stored for 1 week in at 4° C as a concentrated stock solution
- Make new working dilutions daily.

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■ Amoxicillin

- Amoxicillin [A8523 - Sigma-Aldrich.com] (C16H19N3O5S) (FW 365.4)
- Weigh out 0.3654 gms of Amoxicillin
- Dissolve in 80 ml of Tris buffered normal saline at pH 7.4.
- Re-adjust pH to 7.4, bring to 100 ml total volume with buffer.
- Pass through a sterile 0.22 μm filter.
- Aliquot into sterile 1 ml vials @ 0.2 ml/vial.
- Each 100 mls will make 500 unit dose vials.
- Store at -70°C

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- A buffered saline negative control and a histamine (1 mg/ml for prick tests and 0.1 mg/ml for intradermal tests) positive control are placed at the start of each round of tests.
- Drops of each reagent are placed on the outer surface of the upper arm and pricked using a different DUOTIP-TEST® device for each drop.
- Following a 15 minute waiting period, skin prick reactions are read and recorded.
- The mean diameter of the wheal over the mean diameter of the flare or surrounding erythema is measured in millimeters.

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- Positive responses consist of a wheal of 5 mm or more in diameter with surrounding erythema greater than the wheal, a negative response to the control solution, and a positive response to histamine.
- If all tests are negative by skin prick then intradermal (ID) testing is performed using the outer surface of the other upper arm.
- Using the same reagents, 0.02 mls of each reagent is administered ID through individual 27 gauge tuberculin syringes.
- ID tests are also read and recorded after 15 minutes.

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- Positive responses consist of a wheal of 5 mm or more in diameter with surrounding erythema greater than the wheal, a negative response to the control solution, and a positive response to histamine.
- If any puncture test was positive, no ID tests are done with any of the remaining negative reagents.

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- **Penicillin Skin Testing**
- **Data collection Sheet**
- **Allergy Department**

- Penicillin skin test individuals with a history of an adverse reaction that is potentially IgE mediated. Do not penicillin skin test if there is a history of a blistering rash, oral lesions, drug induced anemia or hepatitis associated with a penicillin class antibiotic exposure, or if no history of penicillin exposure. Penicillin skin testing is not useful in evaluating cephalosporin associated reactions. Do not penicillin skin test if a penicillin class antibiotic has been used and tolerated since the index reaction.

- Test performed by: _____ Test ordered by: _____
- Last Name: _____ Patient #: _____
- First Name: _____ Date of test: ____/____/____
- Date of birth: ____/____/____ Gender: (M / F)
- Date of index penicillin adverse reaction: ____/____/____
- Infection index penicillin used for: (URI, otitis media, sinusitis, pneumonia, skin, VD, other list _____)

- Route of administration: (oral / parenteral)
- Time to onset: (< 1 hour / 1-24 hours / 25 – 72 hours / > 73 hours)
- Type of index reaction: (fixed rash, lesions > 24 hours / hives, lesions < 24 hours / angioedema / shortness of breath / hypotension / GI / other list _____)
- Treatment of index reaction: (stopped penicillin only / antihistamine / epinephrine / systemic steroid / other list _____)
- Place and read all puncture tests prior to placing any intradermal tests. Positive tests are defined as wheal ≥ 5 mm with flare > wheal. Do not record test if saline control positive or histamine control negative.

- | ■ Puncture | | ■ Intradermal | |
|--------------------------------------|------------------|--------------------------------------|------------------|
| Time placed: _____ | Time read: _____ | Time placed: _____ | Time read: _____ |
| 1) Penicilloyl-polylysine _____/____ | | 6) Penicilloyl-polylysine _____/____ | |
| 2) Penicillin (0.01M) _____/____ | | 7) Penicillin (0.01M) _____/____ | |
| 3) Amoxicillin (0.01M) _____/____ | | 8) Amoxicillin(0.01M) _____/____ | |
| 4) Buffer Control _____/____ | | 9) Buffer Control _____/____ | |
| 5) Histamine _____/____ | | 10) Histamine _____/____ | |

- Skin test reaction: (None / list _____) Treatment given (None / list _____)
- Oral Challenge: (Penicillin 500mg, Amoxicillin 250mg) Time: _____
- Challenge reaction: (None / list _____) Time of onset: _____
- Treatment given: (None / list _____)
- Delayed reaction reported: (None / list _____) Time to onset: _____

Antibiotic Allergy Incidence

	Males (95% CI)	Females (95% CI)	p values
Sulfa class	2.23% ^a (1.91, 2.59)	3.42% ^a (3.13, 3.74)	< 0.0001
Penicillins	1.11% ^b (1.01, 1.24)	1.45% ^b (1.34, 1.57)	< 0.0001
Tetracyclines	0.47% ^d (0.36, 0.62)	1.27% ^d (1.11, 1.46)	< 0.0001
Cephalosporins	0.60% ^d (0.49, 0.72)	1.08% ^d (0.96, 1.21)	< 0.0001
Macrolides	0.52% ^d (0.38, 0.72)	1.34% ^c (1.13, 1.58)	< 0.0001
Quinolones	0.52% ^d (0.42, 0.65)	1.01% ^d (0.89, 1.14)	< 0.0001

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